Pharmacokinetics and Pharmacodynamics of Rivaroxaban in Bariatric Surgery

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Background I

- Obesity is a risk factor for the development of venous thromboembolism (VTE)
- Incidence of symptomatic deep vein thrombosis (DVT) ranges from 0%-5.4 %
- Incidence of pulmonary embolism (PE) ranges 0%-6.4 %

- VTE (extended) chemoprophylaxis is recommended
- No high evidence for **type, dose, or duration** of VTE prophylaxis (low-molecular-weight heparin)

Philip R. Schauer et al. 2015 SOARD
Escalante-Tattersfield T et al. 2008 SOARD

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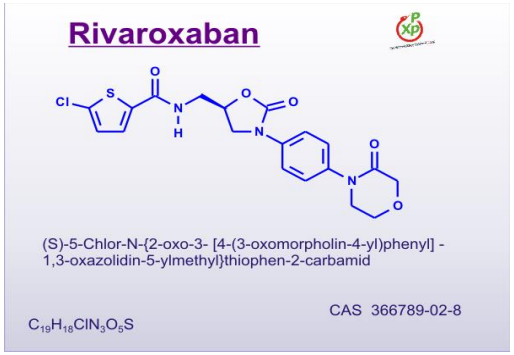
Background II

- Rivaroxaban (Xarelto®) is a new **oral** anticoagulant (NOAC) that directly inhibits factor Xa
- It has proven to be **safe** and **effective** in the (extended) prevention of venous thromboembolism after total hip or knee replacement
- Until now there is no systematic investigation of Xarelto® in obese patients undergoing bariatric surgery

Alexander G G Turpie et al. 2009 Lancet

Kubitza et al. 2005 Clinical Pharmacodynamics



Aim of the study

- To investigate pharmacokinetic (PK) and pharmacodynamic (PD) parameters of Rivaroxaban in the perioperative bariatric setting.

This trial investigates a new indication, i.e. thrombosis prophylaxis in bariatric surgery and it could be an alternative option to LMWH prophylaxis.

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Objectives

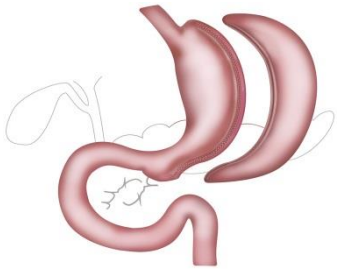
Primary objectives

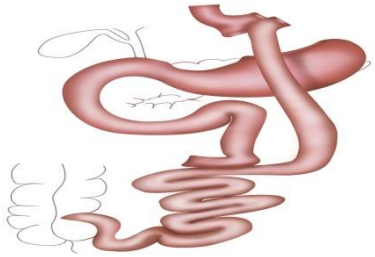
To compare the PK of single doses of 10 mg rivaroxaban in patients before and after two different bariatric surgery procedures

Secondary objectives

– To assess the PD before and after bariatric surgery

– To assess the safety and tolerability after Sleeve Gastrectomy and Roux-en-Y gastric bypass





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Outcomes

Pharmacokinetic parameters

- Area under plasma concentration curve (AUC) pre versus post bariatric surgery
- Maximum plasma concentration (Cmax) before and after bariatric surgery
- Time of maximum plasma concentration (Tmax) before and after bariatric surgery

Pharmacodynamic parameters:

- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)
- Prothrombin fragments (F1+F2)
- Thrombin-antithrombin-complexes (TAT)
- D-Dimers
- Thrombin generation

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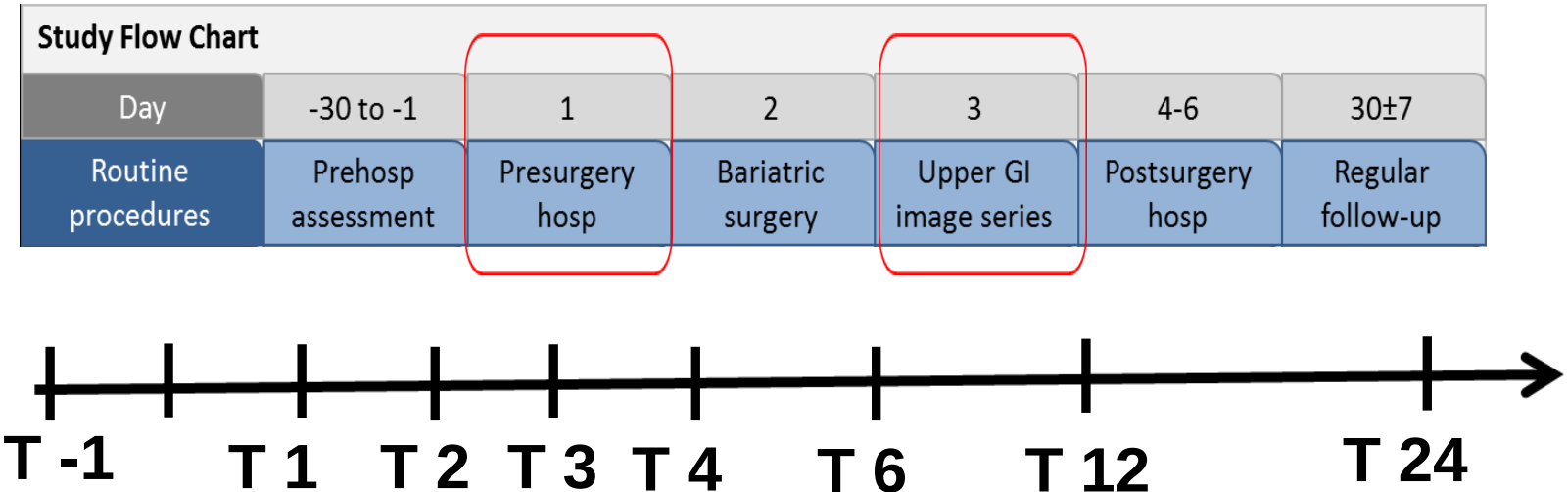
Study Design und Procedure

- Open label phase 1 clinical trial
- Intervention: 10 mg rivaroxaban as a single application before and after bariatric surgery
- Objectives: to assess PK/PD and safety parameters of rivaroxaban in this specific study population.



Inclusion criteria

- Scheduled elective bariatric surgery: laparoscopic Roux-en-Y gastric bypass surgery or sleeve resection
- 18 years and older
- BMI ≥ 35 kg/m^2
- Women of child-bearing age: Willingness of using a double barrier contraception method during the study
- Written, informed consent

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Exclusion criteria

- TVE in history
- Myocardial infarction, transient ischemic attack or stroke within 6 months of study entry
- Severe hypertension
- Severely impaired hepatic or renal function (creatinine clearance <30 mL per min)
- Concomitant use of drugs that strongly inhibit cytochrome CYP3a4, such as protease inhibitors or ketoconazole
- …

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Results Baseline characteristics

	gastric sleeve	Roux-en-Y bypass
n	6	6
Age (mean (sd))	39.33 (9.71)	39.82 (8.30)
Gender = male (%)	3 (50.0)	2 (33.3)
Weight at hospital admission (mean (sd))	135.50 (14.57)	105.67 (11.04)
Height (mean (sd))	174.50 (8.46)	165.50 (5.32)
BMI (mean (sd))	44.57 (4.72)	38.53 (2.81)
ASA (mean (sd))	3.00 (0.89)	2.33 (0.52)
Ethnicity = Caucasian (%)	6 (100.0)	6 (100.0)

Table 1: Baseline characteristics in PP set.

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Results PK Roux-en-Y gastric bypass

	before surgery	after surgery	ratio before surgery/after surgery
AUC (µg * h/L)	753.5 / 13.8	755 / 13.8	1 [0.94;1.06]
AUCnorm (g * h/L)	7927 / 23.3	7942.9 / 23.3	1 [0.94;1.06]
Cmax (µg/L)	136.5 / 10.7	110.8 / 10.7	1.23 [0.91;1.66]
Cmaxnorm (g/L)	1436.2 / 10.4	1165.7 / 10.4	1.23 [0.91;1.66]
HL (h)	4.7 / 27.5	6.3 / 27.5	0.74 [0.5;1.09]
V_Z/f (L/kg)	0.6 / 52.8	0.8 / 52.8	0.77 [0.57;1.04]
Tmax (h)	1.5 (0.9-4)	2.5 (1-4)	

Table 3: Pharmacokinetic parameters for patients undergoing Roux-en-Y bypass surgery; before and after surgery the geometric mean and the coefficient of variation is presented. For Tmax the median and the range is presented. The ratio before surgery/after surgery is presented together with its 95% confidence intervall.

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Results PK Gastric Sleeve

	before surgery	after surgery	ratio before surgery/after surgery
AUC (µg * h/L)	794.3 / 9.5	950.8 / 9.5	0.84 [0.66;1.06]
AUCnorm (g * h/L)	10709.1 / 17.2	12818.5 / 17.2	0.84 [0.66;1.06]
Cmax (µg/L)	135.3 / 26.7	170 / 26.7	0.8 [0.59;1.08]
Cmaxnorm (g/L)	1824 / 32.5	2292.2 / 32.5	0.8 [0.59;1.08]
HL (h)	3.9 / 43.9	4.7 / 43.9	0.83 [0.47;1.47]
V_Z/f (L/kg)	0.4 / 60.6	0.4 / 60.6	0.87 [0.34;2.22]
Tmax (h)	1.5 (1-4)	1.5 (1-4)	

Table 4: Pharmacokinetic parameters for patients ungergoing gastric sleeve surgery; before and after surgery the geometric mean and the coefficient of variation is presented. For Tmax the median and the range is presented. The ratio before surgery/after surgery is presented together with its 95% confidence intervall.

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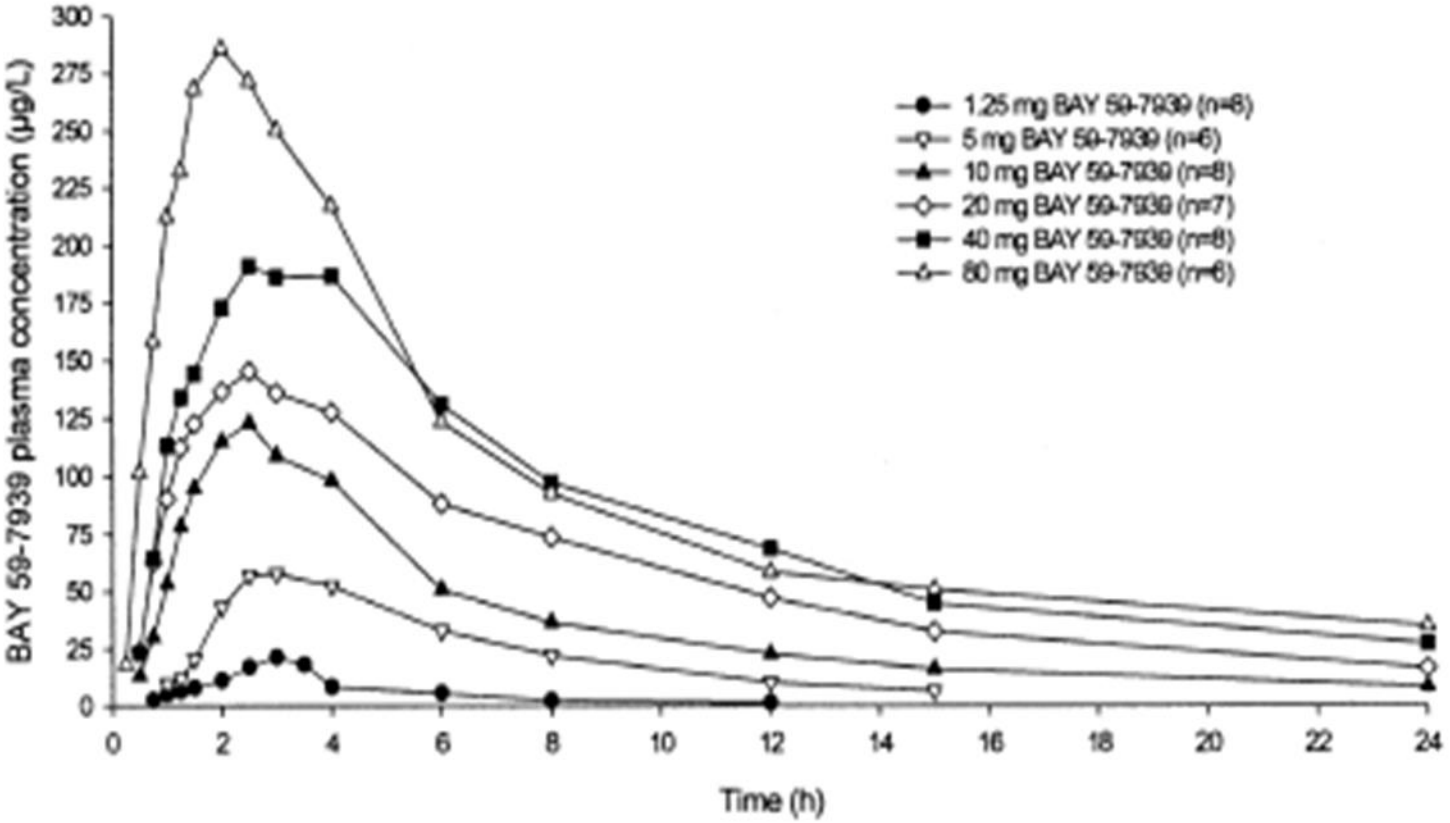
Plasma concentration–time profiles for 1.25 to 80 mg in healthy subjects



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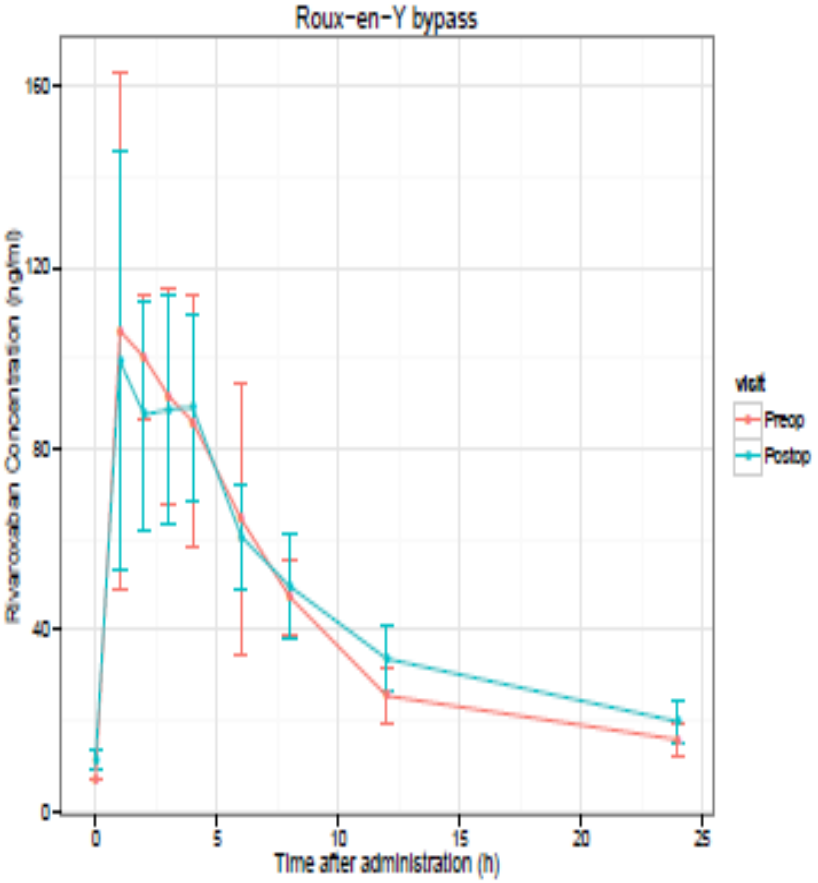
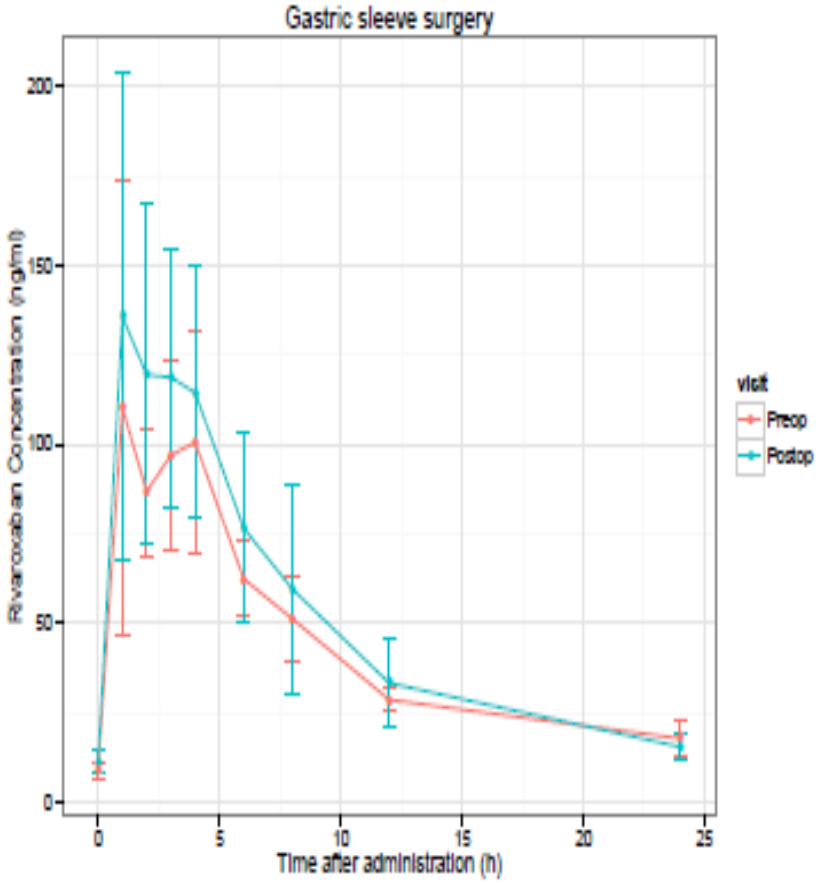
Results PK Roux-en-Y-gastric bypass and Sleeve





Rivaroxaban concentration by type of surgery

Safety analysis

- No major bleeding
- Most common AEs were nausea and headache
- One serious adverse event (SAE) due to a surgical complication which resulted in study discontinuation

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Conclusion

- Rivaroxaban was well tolerated and safe
- There was no significant difference in pharmacokinetic parameters before and shortly after bariatric surgery independent of the bariatric procedure (SG or RYGB).
- Resorption of rivaroxaban was rapidly and not significantly impaired by bariatric surgery

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Outlook

- Based on these results rivaroxaban can be investigated in a phase 2 clinical trial in the perioperative bariatric setting
- “Extention study” accepted by KEK and SWISSMEDIC
- Therapeutic dose of rivaroxaban (20 mg) in high risk patients with preexisting anticoagulation therapy
- Evaluation in the postoperative setting of other visceral surgery patients, especially for extended treatment after abdominal cancer surgery

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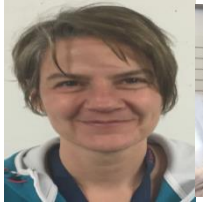
Thank you

The X Factor









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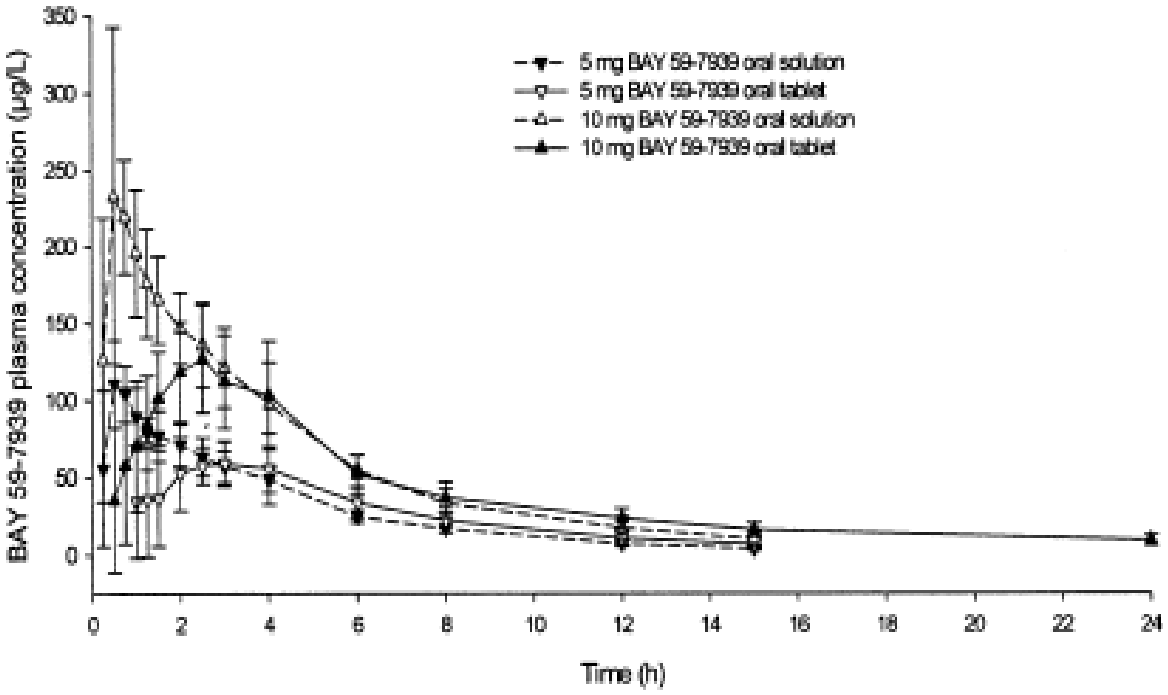

Fig 5. Plasma concentration–time profiles of BAY 59-7939 after administration of BAY 59-7939 tablets (data not shown for 15-, 30-, and 60-mg tablets) (**A**) and 5 and 10 mg BAY 59-7939 as oral solution or tablet (**B**). Data are geometric means.